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A REVIEW ON BIOCHEMICAL CHANGES IN COVID-19 PATIENTS

Biochemistry

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ABSTRACT

The outbreak of COVID-19 caused by SARS CoV-2 virus began in December 2019 in Wuhan city of China and it rapidly spreaded all over the world and declared pandemic in march by WHO. It is predominantly a respiratory disease and causes severe acute respiratory syndrome but now it is known to affect multiple organs of the body and responsible for different clinical features and biochemical changes in body. Different studies on laboratory changes in COVID-19 are published and this keeps growing everyday, there is a need of more research on the laboratory changes and pathophysiology of the disease. A systematic literature search was performed on biochemical changes in COVID-19. Our review results suggested that several inflammatory biomarkers such as IL-6, ferritin, CRP, lactate dehydrogenase (LDH), D-dimer and Procalcitonin (PCT) were significantly raised in COVID-19 infection. Some of biochemical markers (AST, ALT, ALP, LDH) have a significantly higher level in severe cases, and rise in level of these parameters was comparatively less in patients with mild infection. Based on literature search and review results it is suggested that many biochemical parameters of blood may be useful predictors of COVID-19 disease severity. These parameters help in monitoring of COVID-19 disease progression and thereby useful in improving the recovery rate.

KEYWORDS

COVID-19, SARS CoV-2, biochemical changes, inflammatory markers.

INTRODUCTION

In December 2019 few cases of pneumonia were reported from Wuhan city of China and initially it was called Wuhan Pneumonia. Later causative agent identified by genome sequencing revealed that this is a virus of Coronavirus family and termed as SARS-CoV-2 by the International Committee on Taxonomy of Viruses (ICTV) and WHO termed this disease as Corona Virus Disease (COVID-19) [1, 2]. From Wuhan this infectious disease spreaded all over the world and current situation of the disease at the time of this writing is 108 million cases identified and 2.3 million deaths recorded worldwide [3].

Laboratory investigation workup is mainly done for initial screening, assessment of prognosis and for therapeutic monitoring of COVID-19 [4]. Different studies on laboratory changes in COVID-19 are published and this keeps growing everyday, there is a need of more research on the laboratory changes and pathophysiology of the disease. Therefore, a systematic review of different articles based on biochemical changes in COVID-19 and difference in these changes between severe and non-severe cases was done.

METHODS

A systematic literature search was performed in PubMed using following keywords: COVID-19 virus, coronavirus disease 2019 virus, SARS-CoV-2, SARS2, 2019-nCoV, biochemical markers, biochemical and hematological changes, laboratory changes. Articles published in English up to 13 february, 2021 were included.

REVIEW RESULTS

Inflammatory biomarkers

Various articles are published on inflammatory changes in COVID 19 and our review results suggested that several inflammatory biomarkers like cytokines such as IL-6, IL-2, IL-7, ferritin, CRP, lactate dehydrogenase (LDH), TNF-α, interferon (IFN)-γ, procalcitonin (PCT) and erythrocyte sedimentation rate (ESR) were studied and revealed significantly raised level of these biomarkers in COVID-19 infection.

CRP (C-Reactive Protein) is an early inflammatory biomarker in COVID-19, its levels increases significantly at the early stage of the disease, and a positive correlation between increased CRP levels and disease severity has been described [5, 6]. A retrospective study from Wuhan reported that patients with severe disease showed significantly higher level of CRP compared to the non-severe patients (57.9 mg/L Vs 33.2 mg/L, $P < 0.001$) [7]. Liu F. et al in a retrospective study noted that patients with CRP levels >41.8 mg/L were associated with poor prognosis of COVID-19 disease [8]. Elevated CRP level is more sensitive biomarker in early course of disease compared with ESR, NLR (neutrophil-lymphocyte ratio) and CT scan score. Further studies on the CRP revealed it as an excellent biomarker because the 'area under curve' in the receiver operating analysis was 0.87 (95% CI, 0.10–1.00) and sensitivity was 83% and specificity 91%. In a study CT scan score was compared with CRP values and it was noted that CRP values were more significant for earlier identification of disease severity [9]. Various studies have revealed that level of IL-6 rise significantly in severe COVID-19 disease [10]. Raised IL-6 level has a significant role in monitoring of progression of COVID 19 however, since most studies are observational type, there is need of further research on it. A meta-analysis of 1302 patients and of six studies reported that mean IL-6 level was 2.9-times raised in patients with complicated COVID-19 compared to those with non-complicated COVID-19 disease (95% CI, 1.17–7.19) [11]. This study showed significance of IL-6 as an important biomarker because elevation in IL-6 level was correlated with disease severity. Our review showed significantly greater increase in IL-6 level in non-survivors group compared to survivors group.

Lactate dehydrogenase (LDH) may be a significant predictive inflammatory biomarker of severe COVID-19 infection. Mo P. et al reported in a study that LDH level was significantly higher in refractory COVID-19 patients compared to patients with mild infection [12]. One single centre study outside Wuhan involving pneumonia cases was conducted and found statistically significantly raised level of LDH in ICU patients than general ward patients (248 U/L Vs 151 U/L, p=0.002) [13]. In another multi-centre study reported positive correlation of LDH level with extent of organ damage and inflammation [14]. In a study LDH levels were correlated with CT scan score, positive correlation was observed between LDH level and CT scan score and higher LDH levels reflected the severity of pneumonia [15]. Serum ferritin is another important inflammatory marker, its level also showed significant rise in severe form as compared to non-severe form of COVID-19. Procalcitonin (PCT) levels are commonly within the normal range in COVID-19 patients and other viral infections, particularly in initial stage of disease. A metaanalysis reported that increasing PCT level indicates evolution towards severe COVID-19. The significant increase of PCT in severe disease is due to bacterial co-infection, but this should be confirmed with further studies [16]. IL-10 is an anti-inflammatory interleukin and it is significantly elevated in severe COVID-19 patients and higher level are associated with poor prognosis [17].

Coagulation Markers

Our review results noted that studies about coagulation parameters in

COVID-19 patients, were initially published mainly from China [18, 19]. Prothrombin time (PT) and D-dimer are two important parameters of prediction of prognosis and severity of disease in COVID-19. Different coagulation parameters like PT, D-dimer, serum fibrinogen and FDP (Fibrin Degradation Product) were studied in COVID 19 patients and these parameters were compared between non-survivors and survivors. Most studies showed a significantly elevated level of D-dimer and FDP and longer PT in non-survivors compared to survivors. Yu et al. reported in a study that D-dimer level was higher in COVID-19 patients and was associated with poor prognosis [20]. D-dimer level shows positive correlation with inflammatory markers such as IL-6 and CRP. Similar findings were observed in different study of coagulation parameters changes in COVID-19 [17].

Biochemical markers in COVID-19

Various liver biomarkers have been studied in many single centre and multicentre large scale studies in COVID-19. Common liver biomarkers are total bilirubin, Aspartate Transaminase (AST), Alanine transaminase (ALT), Alkaline Phosphatase (ALP), Gamma Glutamyl Transpeptidase (GGT), LDH, and albumin levels. Our results revealed that some of these biomarkers, (AST, ALT, ALP, GGT, LDH) have a significantly higher level in severe cases, and rise in level of these parameters was comparatively less in patients with mild infection. Among these biomarkers severe cases are more likely to have high levels of AST and LDH [21, 22]. A retrospective cohort study reported significantly higher level of ALT, AST, ALP, creatinine, CK and LDH and low level of albumin in deceased patients than in recovered patients [23]. Lei et al observed in a multicenter study that AST is strongly associated with mortality risk in COVID 19, compared to ALT, indicating liver injury [24]. Liver comorbidities in COVID-19 varies from 2% to 11% and during progression of disease 14–53% of patients developed higher level of ALT and AST [34]. COVID-19 liver injury is often transient and resolve spontaneously without any special intervention [25].

Markers of muscular injury creatine-kinase (CK) and myoglobin found significanltly elevated in COVID-19. Cardiac injury is also a common complication in COVID-19 patients. Elevation in troponin level was found in 7-17% of hospitalized COVID-19 patients [26]. Cardiac injury markers like cardiac troponins (cTn) and NT-pro BNP were significantly elevated in patients with severe COVID-19 which is probably due to both viral myocarditis and cardiac injury. Patients with COVID-19 severe disease have high risk for acute kidney injury. Kidney parameters like serum creatinine and serum urea nitrogen are significantly higher in COVID 19 patients and associated with poor prognosis [27].

DISCUSSION

We analysed from our review results that IL-6, serum ferritin and CRP level can be used for monitoring of COVID-19 patients and can assess the outcome of disease. Elevation in the level of these parameters shows the development of a systemic inflammatory response syndrome (SIRS) in patients with a severe disease. During the course of disease different inflammatory cytokines such as IL-6 and other shows exaggerated increase. This is called “cytokines storm”. These cytokines causes damage to many tissue and organs and leads to acute lung injury, acute respiratory distress syndrome (ARDS) and involving many other organs finally causing multiorgan failure MOF [28]. Anti-inflammatory cytokine interleukin-10 (IL-10) was also elevated in patients with the severe form of the disease. It may be related to compensatory anti-inflammatory response (CARS), which can cause higher risk of secondary infections and sepsis as reported in non-survivors [17]. SARS-Cov-2 virus binds with the ACE2 receptor (Angiotensin Converting Enzyme type 2) of target cell and causes internalization of this complex by host cell. These ACE2 receptor are widely distributed in many organs and tissues including lung, liver, intestine, kidney, ovary and testes and produces different clinical manifestation by different tissue damage and multiorgan failure in advanced stage of disease [29]. Liver injury is also produced by immune-mediated inflammation in parallel with the “cytokine storm” [30]. B and T cells lymphocytes also contributes to this inflammation induced liver injury [31].

CONCLUSION

Severe COVID-19 disease causes impairment of several organs and tissues by both direct and indirect effects. This virus can infect cells through the interaction with the ACE2 receptor, which is highly expressed in many organs and tissues. These effects can be assessed by biochemical changes in blood. Our review results suggest that different biochemical markers in COVID -19 are associated with poor outcomes. Most important parameters in prediction of severe COVID-19 are CRP, IL-6, ferritn, LDH, AST, ALT, D-dimer and cTn. Based on literature search and review results it is suggested that many biochemical parameters of blood may be useful predictors COVID-19 disease severity. These parameters help in monitoring of COVID-19 disease progression, reduce mortality and therby useful in improving the recovery rate as well as monitoring of therapeutic intervention. Limitation of the studies is that most of the articles published are based on observational studies and further studies are needed for a better understanding of the pathophysiology and biochemical changes associated with the disease on a larger population group.

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